II. REMARKS

Preliminary Remarks

Reconsideration and allowance of the present application based on the following remarks are respectfully requested. Claims 20-23 are currently pending and remain at issue in this application.

In paragraph 6 of the official action, the examiner objected to the amendments filed November 12, 2002 and June 9, 2003 under 35 U.S.C. §132 because it allegedly introduces new matter into the disclosure. Specifically, the examiner objected the amino acid sequence of cetrorelix as set forth in SEQ ID NO: 1. The applicants respectfully submit that §608.01(p) of the Manual of Patent Examining Procedure (MPEP) states that in order to acquire a proper incorporation of a reference, the application should include an identification of the referenced patent and specific portions of where the subject matter being incorporated may be found. In the present application, page 1, lines 12-16 discuss cetrorelix as a decapeptide with a terminal amide group and reference immediately thereafter U.S. Patent No. 4,800,191 (hereafter the '191 patent). Because the decapeptide amino acid sequence is discussed at page 1, lines 12-16 of the application in conjunction with the '191 patent, the amino acid sequence of cetrorelix could be easily identified in the '191 patent. Thus, the specification "reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention" according to §608.01 (p) of the MPEP. Accordingly, the applicants believe no new matter has been introduced, and therefore, the objection under 35 U.S.C. §132 has been overcome and should be withdrawn.

The applicants do not intend by these or any amendments to abandon subject matter of the claims as originally filed or later presented, and reserve the right to pursue such subject matter in continuing applications.

Patentability Remarks

Rejection Under 35 U.S.C. §112, First Paragraph

In paragraph 8 of the official action, the examiner rejected claims 20-23 under 35 U.S.C. §112, first paragraph, for allegedly lacking proper written description. Specifically, the examiner alleged that the claims disclose an amino acid sequence of cetrorelix that was

not originally disclosed in the claims nor the specification at the time of filing. The applicants respectfully traverse in view of the following remarks.

The applicants submit that the recited amino acid sequence of cetrorelix AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2 has been properly incorporated into the application. As stated above, §608.01(p) of the Manual of Patent Examining Procedure (MPEP) sets forth that in order to acquire a proper incoporation of a reference, the application should include an identification of the referenced patent and specific portions of where the subject matter being incorporated may be found. The specification on page 1, lines 12-16 discuss cetrorelix as a decapeptide with a terminal amide group and references immediately thereafter U.S. Patent No. 4,800,191 (hereafter the '191 patent). Because the decapeptide amino acid sequence is discussed at page 1, lines 12-16 in conjunction with the '191 patent, the amino acid sequence of cetrorelix could be easily identified in the '191 patent. Thus, the specification "reasonably conveys to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention" according to §608.01(p) of the MPEP. Accordingly, the applicants submit the recited amino acid sequence of cetrorelix AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2 is properly described in the specification and claims. In view of the foregoing remarks, the applicants respectfully submit the rejection of claims 20-23 under 35 U.S.C. §112, first paragraph, for lacking written description, has been overcome and should be withdrawn.

Rejection Under 35 U.S.C. §103(a)

In paragraph 9 of the official action, the examiner rejected claims 20-23 under 35 U.S.C. §103(a) as allegedly being obvious over DD411996 (hereinafter Wolf *et al.*) and U.S. Patent No. 5,198,533 (hereinafter Schally *et al.*) in view of Behre *et al., J. of Clinical Endocrinology and Metabolism* 75:393-398 (1992) (hereinafter Behre *et al.*). Specifically, the examiner alleged that the prior art teaches a method for preparing LHRH, which is similar to cetrorelix, an antagonist analog of LHRH/GnRH. The examiner further asserted that Schally *et al.* teaches the same sequence as claimed by the applicants. The examiner alleged that because cetrorelix is a small peptide similar to LHRH, Wolf *et al.* teaches the same method in preparing the sterile LHRH lyophilizate as claimed by the applicants. Accordingly, the examiner alleged that the combination of the prior art teaches the same

claimed invention except the specific cetrorelix concentration of 3% and the specific pH range of 2.5 to 3.0. These values, according to the examiner, would have been obvious to one having ordinary skill in the art at the time the invention due to routine skill (i.e., the determination of the most appropriate cetrorelix concentration to avoid clogging up the filters and determine to correct pH range). The examiner concluded that the claimed invention is *prima facie* obvious in view of the prior art absent any convincing evidence to the contrary.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the reference themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or reference when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicants' disclosure. In re Vaeck, 947 F.2d 488 (Fed. Cir. 1991).

The examiner bears the burden of establishing a *prima facie* case of obviousness and "can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 5 U.S.P.Q.2d 1598 (Fed. Cir. 1988). To support a conclusion that a claimed composition is obvious, either: (a) the references must expressly or impliedly suggest the claimed composition to one of ordinary skill in the art, or (b) the examiner must present a convincing line of reasoning as to why a person of ordinary skill in the art would have found the claimed invention to have been obvious in light of the teachings of the references. *Ex parte Clapp*, 227 U.S.P.Q.972, 973 (Bd. Pat. App. & Inter. 1985).

The applicants submit that Wolf *et al.* and Schally *et al.* either alone or in combination with Behre *et al.* neither teach nor suggest the applicants' claimed invention, *i.e.*, a method for the preparation of a sterile Cetrorelix lyophilizate, said method comprising the steps of dissolving Cetrorelix having the amino acid sequence of AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2 in aqueous acetic acid to form a solution, wherein the acetic acid has a pH range between 2.5-3.0, diluting said solution with water for injection, adding bulking agent to the solution, sterile filtering, dispensing into injection vials, and lyophilizing the solution, thereby obtaining a sterile cetrorelix lyophilizate.

The applicants submit that the combination of the unique cetrorelix amino acid sequence as claimed and the specific conditions for preparing the sterile cetrorelix lyophilizate are neither taught nor suggested by either Wolf *et al.*, Schally *et al.* in view of Behrle *et al.* The examiner specifically alleged Wolf *et al.*, the primary document, teach methods of preparing lyophilized synthetic LHRH using mannitol as the bulking agent and acetic acid as the buffer. With regard to Wolf *et al.*, there is no teaching or suggestion for the preparation of the lyophilized LHRH preparation using the modified LHRH antagonist cetrorelix amino acid sequence AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2. In addition, Wolf *et al.* processed the native LHRH differently. Wolf *et al.* teach first dissolving LHRH in water only as oppose to applicants' use of a 30% acetic acid dissolving solution. Further, Wolf *et al.* provides no teaching as to the difference in filterability or viscosity of the LHRH in water solution. Although Wolf *et al.* used a buffer solution of acetic acid and mannitol in the second step, the optimal pH range in Wolf *et al.* of 3.5 to 4.5 is only achieved by adding 1 N sodium hydroxide solution. No alkaline sodium hydroxide solution is used to establish a pH range in applicants' teaching. The pH range (pH 3.5-4.5 in comparison to 2.5 to 3.0 in applicants' teaching) in Wolf *et al.* is critical because the applicants' claimed decapeptide would gelatinize before filtration using the prescribed preparation steps of Wolf *et al.* In addition, the final sterilized filtrate would be pharmaceutically unacceptable because an alkaline acetic acid salt would be present in Wolf *et al.*'s LHRH lyophilizate (which would be impossible to remove). An alkaline acetic acid salt would not be present in the cetrorelix lypholizate prepared via the applicants' claimed method.

Schally *et al.*, the other primary document, neither teaches or suggests dissolving cetrorelix in acetic acid, diluting the dissolved cetrorelix in a water/mannitol buffer agent, or filtrating/lyophilizing the solution to remove the acetic acid. The applicants' specific (and claimed) preparation steps are designed for use of the particular and unique amino acid sequence of cetrorelix. Schally *et al.*'s method was applied to a number of different LHRH antagonist wherein the solubility was not discussed. The applicants submit the unique amino acid sequence AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2 combined with the use of acetic acid, provided the unexpected result wherein the claimed decapeptide easily dissolved in solution. This solution was filtered and lyophilized to form a pharmaceutically acceptable cetrorelix lyophilizate that completely suppresses LH surges and premature ovulation. Even though Schally *et al.* teaches the sequence, Schally *et al.* teaches dissolving the LHRH antagonist in water only to form a wet granulation. Schally *et al.*

neither teaches or suggests the use of acetic acid in the dissolving step of cetrorelix. One of skill following the dissolving, buffering and purification steps of either Wolf *et al.* or Schally *et al.* would not achieve the same pharmaceutically acceptable product as discovered by the applicants. Thus, one of skill in the art, studying the disclosure of either Wolf et al. or Schally *et al.* in view of the contradictions, would have no suggestion of dissolving cetrorelix of the unique amino acid sequence AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2 in aqueous acetic acid to form a solution, wherein the acetic acid has a pH range between 2.5-3.0, diluting said solution with water for injection, adding bulking agent to the solution, and sterile filtering, dispensing into injection vials and lyophilizing the solution, thereby obtaining a sterile cetrorelix lyophilizate.

Behre *et al.*, the secondary reference, fails to overcome the shortcomings of Wolf *et al.* and Schally *et al.* Specifically, Behre *et al.* neither teaches nor suggests using acetic acid in the **first step to dissolve cetrorelix to prevent gelatinization of cetrorelix**. As admitted by the examiner, Behre *et al.* is cited only to show that cetrorelix is an LHRH antagonist and that it can be prepared in the same manner as LHRH. The applicants submit Behre *et al.* teach dissolving cetrorelix in water supplemented with mannitol. Again, the applicants' method is directed to the combination of the specific amino acid sequence AC-D-Nal(2)-D-pCl-Phe-D-Pal(3)-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2, with the unique preparation steps. The preparation steps taught in Behre *et al.* would result in a similar pharmaceutically inferior cetrorelix lyphoilizate as taught by Wolf *et al.* or Schally *et al.* Accordingly, the applicants respectfully submit that one of skill in the art would not find any suggestion of using acetic acid solution at the specific claimed cetrorelix concentration of 3% and pH range of 2.5 to 3.0 in view of the teachings of Behre *et al.*

In summary, the applicants submit that Wolf *et al.* and Schally *et al.* in view of Behre *et al.* neither teach nor suggest the applicants claimed invention. Accordingly, without such teaching or suggestion, the examiner has not established a *prima facie* case of obviousness. Therefore, withdrawal of the rejection of claims 20-23 under 35 U.S.C. §103(a) is respectfully requested.

III. CONCLUSION

In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains at issue which the examiner feels may be best resolved through a personal or telephone interview, please contact the undersigned at the telephone number listed below.

Respectfully submitted,
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